REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

This Amendment and Reply is being resubmitted in response to the Notice of Noncompliance dated January 17, 2008. This Reply is identical to the Reply filed October 19, 2007 with the following changes:

> Claim 39 has been amended to depend from claim 38, and claims 40 and 41 have updated status as having been previously presented.
>
> In the Remarks section, this amendment to claim 39 and status update to claims 40 and 41 is referenced on page 14 of this Reply in section (iv).

Claims 1, 3, 7-10, 12-14, 16-19, 21, 37, 39 and 45-53 are currently being amended. No new matter is being added.

Claim 1 has been amended to replace reference to the promoters being "active at the same phase in the herpes viral life cycle" with reference to the promoters being "all immediate early, all early or all late promoters." The amendment to claim 1 finds basis in the paragraph bridging pages 23 and 24 of the application as published as WO 2004/029258. The same amendment has been made to claim 37.

Claim 1, part (a) has been amended to specify that the coding sequences are ones "encoding a polypeptide for expression." This amendment finds basis, for instance, at page 1, first paragraph; page 5, lines 9 and 10; and the paragraph bridging pages 12 and 13, which all make clear that the coding sequences of the construct linked to the promoters of the endogenous gene expression regulatory units encode polypeptides for expression via the promoter.

Claim 1 has also been amended to introduce step (d) specifying that the endogenous gene expression regulatory units are different to one another. The amendment finds basis in previous claim 4, which has been cancelled.

The claims directed to nucleic acid constructs have been amended to refer to "[a]n isolated nucleic acid construct."

Claim 39 has been amended to depend on claim 38 instead of withdrawn claim 36, and dependent claims 40 and 41 have been updated with the status as having been previously presented.

In view of the amendments being made to claim 1, claim 2 has been cancelled.

Claim 19 has been amended to refer to HSV-2. This amendment finds basis at page 24, line 24 and original claim 8.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1, 3, 7-10, 12-14, 16-19, 21, 26-53 are now pending in this application, of which claims 31-36 and 42-44 are withdrawn. Entry of this amendment is respectfully requested.

Claim Objections

Claims 26, 27 and 39 were objected to for not beginning with the article "A". Applicant respectfully traverses this rejection.

It is respectfully submitted that claims 26, 27 and 39 should not begin with the definite article "A". In particular, claims 26, 27 and 39 are directed to a plurality of coated particles, not a singular coated particle, as they refer to "Coated particles" .

The claims in question are therefore submitted to be grammatically correct in their present form and do not require amendment.

Rejection under 35 U.S.C. § 101

Claims 1-4, 7-10, 13-14, 16-19, 21 and 46-53 were rejected under 35 U.S.C. § 101 for allegedly being directed to nonstatutory subject matter. Specifically, the Examiner asserts that "a nucleic acid construct" encompasses products of nature. Applicant respectfully traverses this rejection.

As suggested by the Examiner, the claims have been amended to recite the term "isolated". As the claims clearly do not encompass nonstatutory subject matter, Applicant respectfully requests that the rejection be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-4, 7-10, 12-14, 16-19, 21, 26-30, 37-41 and 45-53 were rejected under 35 U.S.C. § 112, second paragraph for allegedly failing to point out and distinctly claim the subject matter which Applicant regards as the invention. Applicant respectfully traverses this rejection.

(i) Reference to 80% sequence homology in the claims is clear

The Examiner asserts that the phrase "inserting herpes virus genomic nucleic acid or a sequence with at least 80% sequence homology into a vector backbone" of claim 37 is indefinite because no sequence is disclosed in the specification. Applicant respectfully traverses.

The reference to 80% sequence homology in the claims is both clear and definite. Contrary to the Examiner's assertion, the specification does provide illustrative examples of herpes viruses at page 28, second full paragraph and in original claim 7. Example 1 of the application refers to the specific HSV strain HG52 strain of HSV-2 as an illustrative example.

The specification does not list the sequences of herpes viruses as these were publicly available as of the priority date of the present application, as the skilled person would have been well aware. It is also highlighted that the genomes of herpes viruses are substantial in size. For instance, that of HSV-2 is over 150 kb in length. To list the entire sequence of illustrative examples of known genome sequences for herpes viruses would therefore have made the specification unduly long. The inclusion of the sequences was unnecessary, given the public availability of the sequences.

For instance, a printout from the NCBI website is now provided in the supplemental Information Disclosure Statement filed herewith giving a summary for the entry for Genbank Accession Number Z86099, which corresponds to the entire sequence of the HSV-2 genome used in Example 1 and is included in the supplemental Information Disclosure Statement filed herewith. As is apparent from this entry, this sequence has been available in its entirety since 1997. The Examiner's attention is also drawn to the literature publication, Dolan *et al.* (1998) *Journal of Virology*, 72(3): 2010-2021, which was also similarly publicly available and supplies the complete genomic sequence of HSV-2. This reference is also cited in the supplemental Information Disclosure Statement filed herewith. The genomic sequences of herpes viruses were therefore publicly available at the time of the invention.

The skilled person would have been well aware what represented a herpes virus and of the public availability of the sequences for the genomes of various herpes viruses. The skilled person would therefore be able to compare a sequence to see whether or not it has at least 80% homology to such herpes virus sequences. The specification goes into detail at pages 15 and 16 about how sequence homology can be calculated. The passages describe various algorithms and publicly available information for calculating sequence homology. Sequence comparisons could be performed with sequences in databases. The absence of the sequence of herpes viruses in the specification is not therefore does not preclude patentability.

The subject matter of the claims is therefore clear and definite. Applicant respectfully requests that the rejection be withdrawn.

(ii) Definition of the promoters employed

The Examiner asserts that the phrase "where the endogenous promoters of the units are active at the same phase in the herpes virus life cycle" is indefinite for being undefined as to how the promoter is considered active and what the phase of the herpes life cycle is. Applicant respectfully traverses this rejection.

In order to facilitate prosecution, whilst not necessarily agreeing with the rejection raised, the expression "which are active in the same phase in the herpes viral lifecycle" has been deleted. In its place, claim 1 now refers to the promoters being "all immediate early, all early or all late promoters".

It is respectively submitted that amended claim 1 is clear. In particular, it uses the terminology which the skilled person, working in the field of viruses, would have employed at the time of the invention and indeed would still do so today. Indeed, it is noted that the Official Action itself uses the same terminology.

In support of that fact, a copy of Davido *et al.* (1996) *Journal of General Virology*, 77:1853-1863 is now submitted in the supplemental Information Disclosure Statement filed herewith. Davido *et al.* illustrates at page 1853, left-hand column, first paragraph of the introduction section, that the language used in the claims and in particular the reference to immediate early, early and late promoters is the language used in the art in describing herpes viruses, stating that "[d]uring its lytic phase, HSV-1 expresses three temporally regulated classes of genes, immediate early (IE), early and late" [emphasis added]. Thus, the meaning of the promoter types recited in claim 1 would be well understood by the skilled person.

Due to deletion of the term "active", the argument raised in the Official Action regarding this term is rendered moot.

The Examiner also argues that it is unclear how the phases of the herpes virus lifecycle are defined rendering the scope of the claims unclear. In place of that expression, claim 1 now refers to specific promoter types of immediate early, early and late promoters well defined in the art.

The skilled person would therefore fully comprehend the meaning of the claims and hence they are clear. Applicant respectfully requests that the rejection be withdrawn.

(iii) Definition of regulatory units

The Examiner asserts that the phrase "expression regulatory units are immediate early genes" is unclear because regulatory units are not equivalent to genes. Applicant respectfully traverses this rejection.

Claim 3 has been amended to replace reference to the endogenous gene expression units being immediate early genes or early genes with reference to the endogenous gene expression regulatory units "comprising" immediate early promoters or early promoters.

As outlined at page 12, lines 23 and 24 of the present application, gene expression regulatory units comprise promoters and hence the claims are clear. Applicant respectfully requests that the rejection be withdrawn.

(iv) Dependency on a withdrawn claim

The Examiner asserts that claims 38-41 are unclear for being dependent on withdrawn claim 36. Claim 38 depends on pending claim 37. Claim 39 has been amended to depend from claim 38 and dependent claims 40 and 41 have updated as to their status as previously preseneted.

(v) Lack of antecedent basis

The Examiner asserts that claims 14, 16, 17 and 51 lack antecedent basis. Applicant traverses this rejection.

Claim 14 has been amended to correct the claim dependency so that the claim now is dependent on claim 13. The expression "the antigens" in claim 14 therefore has appropriate antecedent basis.

In respect of the rejection to claims 16 and 17, it is respectfully submitted that there is appropriate antecedent basis for reference to "the absent region" in claim 1. In particular,

claim 1, part (c) refers to sequences that are "absent from the construct", *i.e.,* to an absent region.

Claim 51 has been amended to refer to "a herpes virus genome" to address the rejection of improper antecedent basis.

Rejection under 35 U.S.C. § 112, first paragraph, written description

The Examiner has rejected claims 1-4, 7-10, 12-14, 16-18, 21, 26-30, 37-41 and 45-53 under 35 U.S.C. § 112, first paragraph for allegedly lacking written description support. Specifically, the Examiner alleges that the specification fails to disclose sequence information for any herpes virus genome and that this lack of sequence information indicates that Applicant was not in possession of the claimed invention. Applicant respectfully traverses this rejection.

A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.* , 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

It is apparent from the specification as a whole, especially in light of the prior art, that the inventors were in full possession of the invention at the priority date of the present application.

As discussed *supra*, the specification does not list the well-known HSV sequences as the skilled person would be aware of them. In support, Applicant has provided several references in the supplemental Information Disclosure Statement filed herewith, which disclose relevant sequences before the filing date of the present application. Further, the HSV-2 sequence used in the present Examples was also known, as shown in the Genbank entry provided in the supplemental Information Disclosure Statement filed herewith.

Therefore, inclusion of these sequences is unnecessary to show possession of the present invention.

Additionally, the Examiner asserts that there is no evidence of information regarding the structure of other herpes virus genomes or its infectivity. Again, such information was well known in the art. In addition, to satisfy the written description requirement, it is not necessary that the specification include such information that is already well know in the art. As shown in Dolan *et al.*, submitted in the supplemental Information Disclosure Statement filed herewith, extensive comparisons between HSV types and strains had been published at the time of filing the present application. Specifically, Dolan *et al.* compares HSV-1 and HSV-2 gene-by-gene and element-by-element in Tables 1 and 3, including the surface proteins important for infectivity. This reference also compares functional elements of the genome, such as the origin of replication on page 2011, first column. Further, this reference teaches the sequences of genes from various strains of HSV-2 in Table 2. Overall genomic structure is given in Figure 2. Indeed, Dolan states "it might well turn out to be the case that there are no HSV-1 or HSV-2 genes that lack a homolog in the other virus" on page 2019, beginning of the last paragraph of the first column, further underscoring the structural and sequence similarities among herpes viruses. Therefore, Applicant submits that there was *extensive* information known about herpes viruses and the relationship between them on the functional, structural and sequence levels. Inclusion of such comparisons in the specification in this case is unnecessary and repetitive.

The Examiner argues that the specification does not provide representative examples of herpes viruses or functional assays. However, that is not the case. Example 1, at pages 52 and 53 of the specification uses the HG52 HSV strain as an illustrative example of how a construct of the present invention can be assembled. Example 1 goes into depth as to how the final construct was generated using specific restriction digests and describes the cloning strategy. Example 2 describes the same process for HSV-1. The Examples therefore show that the inventors were in full possession of the invention and had generated specific constructs for use in the invention.

The description also describes how constructs of the invention can be generated in detail. The description discusses in detail over pages 34 to 41 how genomic fragments can be obtained from the genomes of viruses and how redundant sequences can be removed. These passages further illustrate that the inventors were in full possession of the invention and describe in detail how the invention can be put into practice in the specification.

In addition, in respect of the reference in the claims to sequences with at least 80% homology, as discussed *supra*, the specification refers to appropriate methods for calculating sequence homology. The inventors therefore illustrate how to identify fragments with appropriate sequence homology.

Thus, the application is in full compliance with the written description requirements. Applicant respectfully requests that the rejection be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1-4, 7-9, 12-14, 16, 17, 21, 26-30, 37-41 and 45-49 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Roizman *et al.* (U.S. Pat. No. 5,288,641) as evidenced by Leopardi (U.S. Pat. No. 5,876,923). Specifically, the Examiner alleges that Roizman teaches a herpesvirus genome with a foreign gene under the control of promoter regions of the genome as a vector for the expression of foreign DNA. Further, the Examiner asserts that Leopardi *et al.* teaches particle-mediated delivery of DNA. Applicant respectfully traverses this rejection.

An anticipation rejection under 35 U.S.C. § 102 requires a showing that each limitation of a claim is found in a single reference, practice or device. *See In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985). In order for a reference to be anticipatory, it must "be enabling and describe the applicant's claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *See In re Paulsen*, 30 F.3d 1475 (Fed. Cir. 1994). Applicant asserts that the cited references do not anticipate the present claims as they do not teach each and every element of the claims.

(i) The crux of Roizman et al. is to employ a whole viral genome as a vector whereas the present invention employs vectors comprising fragments of an overall viral genome

Roizman *et al.* is concerned with introducing foreign genes into whole viral genomes for the expression of the foreign gene. This is apparent from the Summary of the Invention section at column 1, lines 43-48 of Roizman *et al.*, which states that:

> According to the present invention, a foreign gene is inserted into a viral genome under the control of promoter-regulatory regions of the genome; the viral genome thus becomes a vector for expression of the foreign gene in infected cells.

[emphasis added].

Roizman *et al.* is therefore concerned with something very different from the present invention, where sub-genomic fragments from the genome of a herpes virus are employed, *i.e.*, much smaller portions of the overall viral genome. The end-goal of Roizman *et al.* is to use the whole virus to carry a single foreign gene. This goal is diametrically opposite to the present invention, where a plurality of genes are expressed from a fragment of the genome.

By using the whole viral genome, the constructs of Roizman *et al.* will express all proteins of the virus. Some of the proteins expressed may well have a detrimental effect if the construct is used in vaccination. For instance, if used in vaccination, some viral proteins may down-regulate the immune system of the vaccinated subject, reducing the efficacy of the constructs at eliciting an immune response against the chosen antigen. Using the whole viral genome also results in much larger, unwieldy constructs, which are harder to manipulate as compared to those of the present invention.

Roizman *et al.* and the present invention therefore adopt diametrically opposite approaches. Roizman *et al.* uses the whole virus to deliver a single gene, with all the drawbacks that entails. In contrast, the present inventors stepped away from the dogma of using the entire virus and use a much smaller sub-region. Furthermore, they express multiple genes from the fragments.

(ii) The shuttle vectors referenced in Roizman et al. do not have two endogenous gene expression regulatory units as specified by the claims of the present application

One of the key features of the present invention is that several coding sequences are expressed from promoters that are naturally expressed at the same time. This feature is reflected in the language of the claims now under consideration, which specify that the promoters of the endogenous gene expression regulatory units are "all intermediate early, all early or all late promoters".

In the viral life cycle, various immediate early, early and late promoters are all expressed in a coordinated fashion. Thus, for instance, immediate early promoters are all expressed together and have co-evolved together as to be compatible for being expressed together. Furthermore, the claims of the present application have also been amended to specify that the coding sequences encode a polypeptide for expression. Therefore, the constructs of the invention express at least two polypeptides.

Roizman *et al.* does not disclose constructs expressing at least two polypeptides from promoters that will give rise to expression at the same time and that have co-evolved together for co-expression. Roizman *et al.* does employ some subgenomic regions in shuttle vectors. However, the shuttle constructs only carry a single foreign coding sequence, and they are used solely as a bridge to allow eventual insertion of the foreign gene into the whole viral genome.

The shuttle vectors of Roizman *et al.* are vectors that contain the foreign gene to be expressed flanked by regions of viral sequences to allow homologous recombination with the viral genome and hence the introduction of the foreign into the whole viral genome. As set-out at column 2, lines 56-60 of Roizman et al:

> In order to recombine the foreign gene into the virus, it is necessary to have homologous flanking sequences through which the gene would recombine at the desired location and a system for selecting the desired recombinant.

However, the shuttle constructs of Roizman *et al.* significantly differ from the constructs claimed by the present application. In contrast with what is disclosed in Roizman *et al.*, the claims of the present application refer to the presence of at least two endogenous gene expression regulatory units and part (a) of claim 1 specifies that "the promoters are each operably linked to a separate coding sequences encoding a polypeptide for expression" [emphasis added]. At least two polypeptides are therefore expressed from the endogenous promoters. The Examiner cites Figure 4 of Roizman *et al.* as showing such an arrangement. However, neither Figure 4, nor the Roizman *et al.* reference as a whole discloses this multiple polypeptide construct.

The arrangement of the elements in the construct of Figure 4 of Roizman *et al.* is illustrated by Figure 5, which provides a more detailed diagram of how the elements in the vector are arranged. Figure 5 shows the chosen foreign coding sequences encode the Hepatitis B surface antigen (HBsAg). The foreign coding sequences are shown linked to the promoter of the ICP4 gene (PICP4) and will be expressed from that promoter. However there is no second endogenous gene expression regulatory unit linked to separate coding sequences, as specified by the claims of the present application. Figure 5 of Roizman *et al.* shows that the TK promoter is downstream of the HBsAg coding sequences and hence will not drive expression of the HBsAg coding sequences. Furthermore, the HBsAg coding sequences do not represent "separate" coding sequences as specified by the claims, as they are the same coding sequences that are linked to the first endogenous promoter.

That the TK gene and promoter are not active in the construct shown in Figure 4 is illustrated by the fact that Roizman *et al.* selects for loss of TK activity as a way of identifying successful recombinants. The TK coding sequences are not therefore expressed. At most, the construct in Roizman *et al.* expresses a single polypeptide.

Thus, whilst the crux of the present application is that several coding sequences are expressed in a co-ordinated expression with promoters that are all immediate early, all early or all late promoters, Roizman *et al.* is concerned with expressing a single foreign protein and makes no disclosure or suggestion of expressing a second protein in coordinated fashion. The two could not be more different.

Nothing in Roizman *et al.* would have therefore led the skilled person to the subject matter of the invention.

(iii) Leopardi et al. adds nothing to the disclosure of Roizman et al

Leopardi *et al.* is concerned with the use of the herpes protein ICP4 in inhibiting apoptosis. Like Roizman et al, Leopardi *et al.* focuses on a single polypeptide. Nothing in Leopardi *et al.* discloses or suggests the co-ordinated expression of polypeptides from at least two promoters in a genomic fragment from a herpes virus, where the promoters are the same type of viral promoter, as specified by the claims of the present application.

The Examiner cites mention in Leopardi *et al.* of particle mediated DNA transfer. However, in the absence of anything in Leopardi *et al.* or Roizman *et al.* that would have directed the skilled person to generate the constructs of the invention, reference to particle mediated transfer is irrelevant.

Thus, the invention is not anticipated as neither Roizman *et al.* or Leopardi *et al.* disclose the construct type specified by the claims. Applicant respectfully requests that the rejection be withdrawn.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a

check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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